PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
MXI-160PC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/20272	25/07/2000	29/07/1999
International Patent Classification (IPC) or national classification and IPC C07K16/00		
Applicant MEDAREX, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/02/2001	18.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Montrone, M Telephone No. +49 89 2399 8711

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/20272

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-70 as originally filed

Claims, No.:

1-50 as received on 17/08/2001 with letter of 10/08/2001

Drawings, sheets:

1/24-24/24 as originally filed

Sequence listing part of the description, pages:

1-12, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 41 to 47.

because:

   ☒ the said international application, or the said claims Nos. 41 to 47 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1 to 5, 7 to 30, 38 to 50
	No:	Claims	31 to 37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1 to 5, 7 to 30, 38 to 50
Industrial applicability (IA)	Yes:	Claims	1 to 40, 48 to 50
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: WO-A-9700271
D3: WO-A-9802463
D5: J. Clin. Oncology, vol., 14, 1996, p.: 737-744
D6: Exp. Opin. Invest. Drugs, vol. 7, 1998, p.: 607-614

Item I:

There appears to be no basis for the subject-matter of newly filed claims 6, 8 to 13 (with respect to "comprising" and "conservative sequence modifications thereof") and 22 to 27 (with respect to "comprising" and "conservative sequence modifications thereof"). Thus, the amendments appear to go beyond the disclosure of the international application as originally filed, contrary to the requirements of Article 34(b) PCT. Consequently, no preliminary opinion with respect to novelty, inventive step and industrial applicability will be formulated for the subject-matter of said claims.

Item III:

Claims 41 to 47 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(i) PCT).

Item V:

1. Claim 1 refers to an isolated human monoclonal antibody binding specifically HER2/neu and inhibits growth of cells expressing HER2/neu, produced from a transgenic non-human animal.

None of the cited prior art documents discloses an isolated human monoclonal anti-HER2/neu antibody irrespective of how it is produced. D1 refers to human phage-derived anti-HER2/neu single chain antibodies or $(fab)_2$ fragments without referring to complete monoclonal antibodies. Consequently, the subject-matter of claim 1 is

considered to be novel and complies with the provisions of Art. 33(2) PCT. The same applies to the subject-matter of claims 2 to 5, 7, 14 to 17 dependent thereon, the antibodies and hybridomas characterised by the specific sequences referred to in claims 8 to 13 and 21 to 28, the antibodies according to claims 18 to 20, the transgenic non-human animal of claim 29, the method of claim 30, the composition of claims 38 to 40, the method of claims 41 to 48, the nucleic acids of claims 49 and the immunotoxin of claim 50.

However, the bispecific and multispecific molecules of claims 31 to 37 are not considered to be novel for the following reasons:

D3 discloses bispecific and multi specific antibodies binding to Fc receptors, the HER2/neu receptor and/or the EGF receptor (see abstract, page 1, lines 5 to 16). Said antibodies are used as therapeutic agents to cytolyse tumour cells in the presence of effector cells (see page 2, lines 29 to 36; page 3, lines 6 to 10). Moreover, they bind to sites on the FcαR which are different from the binding site for endogenous IgA (see page 3, lines 1 to 6). The antibodies can be humanised or fully human, prepared in transgenic mice (see page 5, lines 10 to 14; page 18, lines 20 to 30). Therefore, D3 is considered to be detrimental to the novelty of the subject-matter of claims 31 to 37.

D1 refers to fully human, phage-derived anti-HER2/neu antibodies having a high binding affinity of about 1.6×10^{-8} to 1×10^{-12}. Moreover, the antibodies are used in the fields of cancer immunodiagnostics and immunotherapeutics (see abstract, page 1, lines 16 to 30, page 2, lines 17 to 20, page 3, lines 10 to 12, page 4, lines 19 to 25 and page 49, lines 1 to 26). The antibodies can be of every isotype and form (see page 2, line 21 to page 3, line 2 and page 5, lines 8 to 14). However, only scFv or $(Fab)_2$ antibodies are mentioned and not complete mabs (see page 30, line 9 to page 31, line 4). Immunotoxins or bispecific antibodies are mentioned (page 3, line 28 to page 4, line 2; page 11, lines 7 to 16 and page 50, lines 19 to 31). A bispecific molecule which binds to HER2/neu and FcγRI is mentioned (page 11, line 14). Recombinant production of said antibodies is mentioned as well (see page 3, lines 13 to 19). Multispecific antibodies are indicated as well (see page 11, line 28 to page 12, line 5. Thus, D1 is considered to be detrimental to the novelty of the subject-matter of claims 31, 32 and 35.

In consequence, the subject-matter of claims 31 to 37 is not considered to be novel and does not comply with the provisions of Article 33(2) PCT.

2. Moreover, the subject-matter of claims 1 to 5, 7 to 30 and 38 to 50 is not considered to be inventive for the following reasons:

D1 is considered to be the closest prior art. Said document already discloses fully human anti-HER2/neu antibodies produced by phage display and their therapeutic or diagnostic use in the treatment of cancer (see point 1, supra for relevant citations). The subject-matter of claim 1 is distinguished therefrom by using an alternative method for the production of human anti-HER2/neu antibodies via transgenic mice.

The objective problem to be solved by the present application was therefore to isolate human anti-HER2/neu antibodies in an alternative manner.

However, the production of high affinity human antibodies in transgenic mice is considered to be a standard technique in the art. The present application indicates itself on page 20, line 28 to page 22, line 1 a lot of scientific and patent literature for using transgenic mice, such as the "HuMAb" or HCO12 for the production of fully human antibodies against any desired antigen. D6 discloses the general advantages of fully human high affinity antibodies produced in transgenic mice, such as reduced immunogenicity or use of the standard mouse hybridoma technology (see abstract, page 607, third para.; page 609, left col., second para.). Different examples of successfully produced human antibodies against human antigens are given, such as a human anti-EGF receptor antibody (see page 612, left col., second para to page 613, right col., first para.). In addition, D3 mentions the production of fully human antibodies by immunising transgenic mice as a standard alternative procedure (relevant citations are mentioned in point 1, supra). In consequence, the person skilled in the art trying to find an alternative way to produce fully human antibodies would have combined the teaching of D1 with D3 or D6 for obvious and straightforward reasons and would have arrived at the claimed subject-matter falling within the scope of claim 1 without employing any inventive skill. Consequently, the subject-matter of present claim 1 does not appear to be inventive and does not fulfil the requirements of Article 33(3) PCT. The same arguments apply for the subject-matter of claims 2 to 5, 7 to 30 and 38 to 50 since the claimed antibody

characteristics are considered to be obvious or not surprising in the light of D1 and D6. Moreover, D5 teaches already the clinical use of a humanised anti-HER2/neu antibody for the treatment of breast cancer (see abstract).

3. For the assessment of the present claims 41 to 47 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI:

The document WO-A-9955367 filed at the 23.04.1999, published at 04.11.1999 and claiming the priority of 24.04.1998 could be relevant to the subject-matter of the present application if the priority of the claims is not valid.

Item VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D3, D5 and D6 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

1. The monoclonal antibodies or hybridomas of "3.F2, 2.E8, 1.D2, 1.B10 and 3.B4" as referred to in present claims 18 and 28 are considered to be mere internal designations without any technical information. Moreover, accession numbers and deposit receipts are missing in the present application. (Article 6 PCT and Rule 13^{bis}.1-3 PCT).

2. The term "fused to an immortalised cell" used in claims 17 and 21 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features

to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

3. The back reference of claim 20 appears to be wrong which renders the scope of said claim unclear (Art. 6 PCT).